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Circular Letters:

Some Current Problems in the Field of Parenteral Nutrition

Although recent developments in the field of parenteral nutrition have done a great deal to improve the care of surgical patients, both before and after operation, they have also created additional problems which must be solved if further progress is to follow. Thus in a variety of surgical situations the parenteral use of protein hydrolysates has helped materially to reduce or to minimize the catabolic loss of tissue nitrogen.

Probably the greatest deterrent to the more general acceptance of the protein hydrolysates is the current necessity of administering them under conditions of inadequate caloric intake, thereby hampering their effective utilization. In fact, the problem of supplying enough calories parenterally to satisfy the energy needs even for maintenance, and more particularly for the reconstruction of new tissue, is a formidable one which is as yet far from being solved. The intravenous use of solutions of glucose makes possible the deposition of glycogen in the liver and elsewhere and thus mobilizes a reserve of energy essential for the processes of tissue protein synthesis. But the caloric needs of an average adult at bed rest are probably in the neighborhood of from 2,000 to 2,400 calories per day, and to satisfy this need by parenteral administration requires quantities of glucose often beyond the assimilatory capacities of the tissues. Concentrations as high as 25 percent have been used, but this adds to the likelihood of injury to veins as well as the degree of glycosuria. Emphasis is being currently placed on the point of view that fructose in invert sugar solution is more readily utilized than glucose, and, in addition, that it is a better precursor of glycogen. But even if this supposition is true, evidence is still lacking that enough additional calories can be assimilated in this way to satisfy the daily needs for protein synthesis. In an effort to augment caloric intake a few investigators have added alcohol to glucose solution, thereby introducing several hundred more calories per day.

All these methods fall short of the caloric goal in most instances, however, and it is increasingly evident that only an emulsion of fat with its higher caloric potentiality can satisfy the daily caloric needs. Fat emulsions of small particle size and of good stability have been developed, and have been given a limited clinical trial without harmful effects and with nutritional benefit. Unfortunately, it has not been possible to prepare emulsions which remain nontoxic for more than a few weeks. Until this is accomplished, the commercial manufacture of such materials for intravenous use will not be feasible.

In the meantime it is possible to administer freshly prepared fat emulsions, properly homogenized, so that injected amino acids may be better utilized. Ravdin and Gimbel have pointed out that, no matter how much protein may be given to a surgical patient, at least 30 calories per Kg. of body weight are essential to achieve nitrogen balance, and in the studies of W. C. Rose dealing with minimal requirements of essential amino acids there were instances in which the caloric needs were as high as 55 calories per Kg. per day. Therefore, unless the caloric intake is adequate there is little reason to expect opti-

mal utilization of parenterally administered amino acids.

Under similar unfavorable circumstances the use of blood plasma as a source of protein nutriment will also be of slight avail because the protein molecules will be burned as fuel rather than used for tissue reconstruction, and to use expensive plasma as a source of calories is obviously an uneconomic metabolic procedure. It is now apparent that until the problem of caloric needs can be solved, about all that can be hoped for in hydrolysate or plasma protein therapy is to accomplish a sort of "holding operation," whereby the loss of tissue nitrogen can be kept at as low a level as possible.

Even when the caloric needs are met, the surgeon is still confronted with the problem of ascertaining which of the hydrolysates now commercially available is of high nutritive quality. A hydrolysate is expected to supply a mixture of essential and nonessential amino acids in amounts and proportions which the tissues can utilize effectively. A comparison of hydrolysates now available reveals a considerable variation in nutritive quality due to differences in modes of manufacture, and an evaluation method is badly needed which can indicate those products which are nutritionally superior when administered parenterally. Unfortunately, there is no way to accomplish this adequately at the present time.

Although all the hydrolysates now on the market are derived from high quality protein, the methods of hydrolysis lead to nutritionally differing products. Those produced by prolonged acid hydrolysis tend to be "complete" in the sense that they have a low peptide content and consist largely of amino acids. Unfortunately, however, prolonged acid hydrolysis destroys the essential amino acid, tryptophan, and this amino acid must later be added to the hydrolysate. But because there is always a chance that complete reconstitution may not be accomplished, such a preparation may be nutritively inferior to others available for clinical use. On the other hand, although enzymatic hydrolysis does not destroy essential amino acids, it does lead to the formation of a "partial" hydrolysate. By this is meant one with a high peptide content, and peptides are not as readily utilized by the tissues as are free amino acids. In the use of partial hydrolysates, therefore, there is a considerable loss of nitrogen by way of the urine, and, in consequence, varying quantities of important amino acids making up the peptide aggregates are lost which otherwise might have been utilized by the tissues. Information is meager as to the relative tissue availability of such peptides under different metabolic circumstances, but evidence at hand at least suggests that a low peptide content is desirable in a hydrolysate provided that in the course of the hydrolysis no serious damage has been done to essential amino acids.

Because of the recognized need for a greater caloric intake, it has become customary to dispense the hydrolysates in a 5 percent glucose solution. This practice has created another problem because sterilization by means of heat and pressure, or merely storage for long periods of time, leads to an interaction between glucose and amino acid molecules. This reaction, now known as the Maillard or "browning" reaction, reveals to some degree the extent of the amino acid-sugar combination. The reaction is serious from a nutritional point of view

because several of the essential amino acids are able to combine with glucose and thus form complexes which are resistant to enzymic degradation. Such a material when used may function as a low-quality protein because of the limiting action of one of more essential amino acids which have become bound to sugar. Some manufacturers have solved this problem in part by sterilizing their products in the absence of heat or pressure, but the problem of storage for long periods still remains. Fortunately, however, this problem can be quickly solved whenever it becomes possible to supply a nontoxic fat emulsion with adequate caloric potentialities.

Another problem now receiving particular attention is related to mineral requirements for the processes of tissue protein reconstruction, especially with reference to the intracellular electrolytes, potassium, phosphate and magnesium. This is a problem of especial nutritive significance because, when there has been a loss of tissue in the course of debilitation, particularly of muscle substance, the process of tissue-protein depletion is necessarily accompanied by a loss of intracellular electrolytes. When an attempt is made to rebuild such depleted tissues it is obvious that the wasted cells will require not only calories and amino acids but also those electrolytes which are normally a part of the internal cellular structure. The usual electrolyte solutions, such as saline or glucose solution, provide no potassium or phosphate; furthermore, the hydrolysates themselves are all more or less deficient in potassium. Nevertheless there is experimental evidence that depleted tissues require these salts for effective protein synthesis. A current problem of considerable interest is to ascertain under what circumstances potassium and phosphate may be supplied in the course of parenteral alimentation. More consideration of these electrolyte needs must be given, particularly because in many conditions in which parenteral nutrition is employed there has already been a marked loss of intracellular potassium.

Finally, parenteral nutrition will not be fully accepted as a therapeutic procedure so long as it is accompanied by the development of nausea, vomiting and depression of appetite. Evidence now available suggests that the tendency to nausea and vomiting is due in large measure to a high content in some of the hydrolysates of glutamic and aspartic acids. In an effort to minimize these undesirable features, Merck and Company have prepared an amino acid solution in which these two amino acids have been replaced by glycine. This product can be injected rapidly into human subjects without causing severe nausea, and it can also maintain nitrogen balance under appropriate conditions. However, it is not yet commercially available, being still in the developmental stage. (Editorial, A. M. A. Arch. Surg., August '51, P. R. Cannon)

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Comparative Utilization of Invert Sugar and Dextrose in Nondiabetic Human Beings

The study of the tolerance of patients to controlled rate infusions of invert sugar and dextrose was undertaken primarily for the purpose of comparing

the assimilation of these sugars by different individuals. It was anticipated that the data which would be obtained would reveal that invert sugar was superior to dextrose for intravenous infusions, and expectations were fulfilled.

The dextrose solutions used were those commonly employed in hospitals in "vacoliter" bottles, and the invert sugar was also supplied in "vacoliter" bottles. The invert sugar preparation is prepared from sucrose by hydrolysis and contains equal quantities of dextrose and levulose. Solutions of invert sugar in distilled water or physiologic saline are stable, colorless, crystal clear, may be stored at room temperature and are nonpyrogenic and nonanaphylactogenic.

The patients used for checking the comparative assimilation of invert sugar and dextrose were nonoperative surgical subjects or convalescing operative patients who were considered to be normal. None were thought to be diabetic, and urine studies as well as total blood sugar estimations before the tests showed normal values. Each test with each sugar was performed in a similar manner and whenever possible in the same patient on different days.

Controlled rate, single infusions were administered at as near 1.5 Gm. per Kg. per hour as was technically possible. Tolerance tests were performed for both invert sugar and dextrose with 50, 100 and 150 Gm. dissolved in distilled water.

The degree of assimilation or utilization for each sugar was calculated by determining the difference between the grams injected and the grams of total glycosuria found in the urine collected during and for a 4 hour test period after the end of the infusions. In the case of the subjects receiving invert sugar the glycosuria was further studied by comparing total glycosuria to degree of levulosuria. The chemical methods employed were: Benedict's quantitative method for total reducing substance in the urine; Roe's colorimetric method for total levulosuria; Folin-Wu's quantitative procedure for total blood-reducing substance and Roe's method for levulosemia.

It was observed that when equal quantities of invert sugar and dextrose are injected intravenously to nondiabetic adults at similar rates, more invert sugar is assimilated at a more rapid rate than is dextrose. Therefore, invert sugar is a better carbohydrate than dextrose for intravenous infusions.

Fifty grams of invert sugar may be given twice as fast (33 minutes) as 50 Gm. of dextrose (62 minutes), and practically all of the injected invert sugar will be utilized, whereas 6 percent of the dextrose will be lost in the urine.

One hundred grams of invert sugar may be given in 1 hour and 97.6 percent will be rapidly assimilated. On the other hand, 100 Gm. of dextrose given in 1 hour will cause glycosuria, which is 6 times greater than that seen with invert sugar and in some instances is equal to a 30 percent loss of the infused dextrose.

When 100 Gm. of invert sugar are infused in the same time as 50 Gm. of dextrose (1 hour), most of the invert sugar is retained by the body and the patient gains an extra 50 grams, receiving twice as much sugar, or 200 more calories. Ten percent invert sugar is the choice for "every day" parenteral carbohydrate therapy.

Of 150 grams of invert sugar injected in 1 1/2 hours, 96.4 percent is assimilated as compared with 88.5 percent for a similar amount of dextrose.

Invert sugar shows the same ability as dextrose to be utilized in unlimited quantities (Allen's "dextrose paradox"). In other words, increasing the amount of sugar infused at a constant rate causes some increased glycosuria, but the amount of sugar retained is much greater. This point of view has been overlooked by many clinicians and should be applied more often if adequate carbohydrate therapy is the goal of the clinician.

A comparison of the degree of dextrosuria to levulosuria during and after the infusion of invert sugar indicates that levulose is removed more rapidly from the blood stream and probably converted to glycogen more rapidly than is dextrose. The data also infer that dextrose in combination with levulose as an invert sugar preparation is utilized in greater amounts and more rapidly than when given alone.

Since more invert sugar is utilized more rapidly than dextrose, the implications are that glycogenesis is more rapid and more complete than with dextrose. This increased hepatic glycogen may have important clinical application in the therapeutic use of invert sugar as a parenteral carbohydrate.

No pyrogenic or anaphylactic reactions were noted throughout this study. No abnormal blood pressure changes were recorded, and no sclerosis of the veins was seen at the rates suggested. (M. Ann. District of Columbia, July '51, J. J. Weinstein)

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Studies on the Blood Supply of Tumors in Man. I. Fluorescence of Cutaneous Lesions

The continued growth of most neoplasms is dependent in part upon the blood supply. The vascularity of some tumors is well known, and at operation excessive enlargement of arteries leading to tumor areas is frequently noted. This report deals with studies in vivo of the afferent blood supply of neoplasms and other lesions in the skin as demonstrated by fluorescein.

Eighteen patients with neoplastic lesions involving, or presenting through, the skin were studied with 37 intra-arterial and 5 intravenous injections of from 3 to 10 cc. of 5 percent fluorescein. The fluorescein was injected rapidly into a major artery leading directly toward the tumor site. The time of appearance and duration of the fluorescence was observed under ultraviolet light. The areas of fluorescence were outlined with indelible ink on the skin under ultraviolet light and after the room was relighted, the relationship to the active lesions was recorded. Usually the dye was injected directly into the femoral or brachial artery; in some instances an intra-arterial catheter was used.

In general, the neoplastic lesions directly involving skin (mycosis fungoides, lymphoepithelioma) began to fluoresce a bright yellow color within 3 to 15 seconds after introduction of the fluorescein into the artery. This color further intensified during the injection period. After 2 to 4 minutes, the normal tissue adjoining the lesions exhibited no fluorescence or only a minimal amount. The

luminescence of the neoplastic lesions lasted for 1 or 2 hours, with the intensity decreasing slightly. The fluorescence of histamine wheals employed as controls, and of the uninvolved skin, disappeared within 20 minutes. Fluorescence of areas and lesions in other parts of the body of these patients was barely discernible. In 2 cases, new metastatic lesions showed moderate uptake of the dye after recirculation. Old necrotic lesions and lesions of Kaposi's sarcoma showed no luminescence. Lesions that had been previously treated intensively by x-ray or nitrogen mustard fluoresced poorly or not at all.

Fluorescein in identical amounts was injected intravenously before, and twice after, 15 mg. of triethylmelamine was administered orally in 1 case, on 3 separate occasions. Initially, the cutaneous lesions showed fluorescence after 90 seconds, with the intensity reaching its maximum 2 minutes thereafter, and persisted for 2 hours. There was a marked decrease in luminescence of the same lesions following the second injection of fluorescein as compared with the initial injection before melamine was administered 5 days previously. The third injection of fluorescein, 29 days later, showed a return to the original fluorescence.

In general, the fluorescence was limited to the neoplastic lesions, closely following their borders. In a few instances, however, there was a discrepancy between the fluorescence and the visible limits of the lesions of mycosis fungoides in that the brilliance of the yellow color varied within the lesions and occasionally was out of the area of a visible lesion. There was no uptake of intravenously administered fluorescein by lesions that were thought to be infiltrations of Hodgkin's disease. It was also possible to prevent fluorescence of an area completely, either involved or normal, by manual pressure, presumably by obliterating the capillaries. In 4 instances there was an absence of fluorescence in areas previously treated with intra-arterial nitrogen mustard.

The disappearance of luminescence after 2 hours was gradual and in proportion to the intensity.

Discussion. Algire has found that proliferation of vascular tissue develops promptly about a neoplasm during its enlargement. Similarly, the arterial blood supply to some neoplasms is greater, in proportion, than to comparable normal tissues of the same volume. One must interpret the findings first, from the time of initial fluorescence and, second, from its later intensification. Since the material was introduced into the largest artery leading into the involved leg, and since in most instances the appearance of the fluorescence in and about the neoplastic lesion appeared within 3 to 15 seconds after the injection was initiated and many seconds before it was seen in the uninvolved areas, it is most suggestive that the afferent blood supply to those neoplastic lesions is increased. The further intensification of the fluorescein is probably due to an altered vascular permeability. That either radiopaque media or fluorescein would reach the neoplastic tissue by arterial administration in greater concentration than uninvolved areas, has already been shown to be true in the vascular patterns demonstrated by arteriography of intracranial and visceral neoplasms. The rapid and apparently selective appearance of relatively large amounts of fluorescein in the lesions

of mycosis fungoides following arterial injection is likewise indicative of an increased arterial blood supply to the involved areas. Such vascularity is not limited exclusively to tumors nor does it occur in all neoplasms, as was demonstrated in these studies.

The persistence of the fluorescence in the lesions, long after it had vanished in the histamine wheals and uninvolved skin, is suggestive of increased capillary permeability within the immediate vascular supply of the lesion. It would appear reasonable to expect an increased diffusion rate and altered capillary permeability to operate mostly during the slower phase of increasing intensity. When any material injected into an artery leading to any tissue appears in greater concentration in the tumor (as judged under direct vision) before it does in the immediate involved area, within a matter of a few seconds, it would appear that it does so because there are larger, and more, channels leading to that tumor.

In 4 instances where the tumor nodules were ulcerated, fluorescent material was easily demonstrated on cotton swabs that had been gently drawn across the surface of the ulcer. Whether this apparent increased permeability of the vessels within the tumor is responsible for the alleged preference of neoplasms for fluorescein or whether the tumor itself exerts some selective influence upon substances circulating through tumor tissue, cannot be proved at present. Some neoplasms show a selective uptake of radiophosphorus (P^{32}), which persists for 24 to 48 hours. Inflammatory lesions of the breast show an even greater differential uptake for radiophosphorus. The increased vascularity and altered capillary permeability of such lesions must be considered in an interpretation of the selectivity of neoplasms for injected materials.

The intensity of the fluorescence appears to be directly related to the amount and concentration of dye that is injected. In addition, lesions supplied arterially with fluorescein in high concentration exhibited luminescence throughout, while lesions beyond the direct arterial blood supply received the fluorescein in much lower concentrations after recirculation and fluoresced proportionately less and then only at the periphery. After 30 minutes to 1 hour, these lesions showed luminescence throughout but always much less in degree than those lesions receiving the dye by direct arterial injection.

The absence of fluorescence of lesions previously treated with x-ray irradiation confirms the fact the x-ray irradiation decreases the vascular supply of a neoplasm, reducing its main nutritional source and consequently curtailing its rate of enlargement or reducing its mass until the necessary level of vascular supply is re-established. Lesions previously treated with intra-arterial nitrogen mustard similarly failed to fluoresce.

Although it has been confirmed that arteries leading to neoplastic areas are frequently enlarged and increased in number, the fundamental cause for this proliferation remains obscure. The vascular proliferation results in an increase of oxygenated blood to neoplasms, which can metabolize under relatively anaerobic conditions. This increase of oxygenated blood thus appears to be unnecessary, and the rate of transfer and utilization of this increased oxygen supply remains

obscure.

The increased vascular reaction about neoplasms appears to be at the advancing edge of the lesion, or in its most active area. Tumors that enlarge rapidly often push back the increased number of capillaries at the periphery so that a pseudocapsule may be formed about the tumor. Central necrotic areas of tumor nodules show little, if any, fluorescence, which may prove avascularity of the tumor and may be responsible for the tissue degeneration. However, some smaller lesions did fluoresce and although they were not as soft as the larger lesions they were probably necrotic.

Cutaneous neoplastic lesions have been observed to be definitely warmer than the surrounding normal tissue, affording additional evidence of their increased blood flow. If such increased arterial proliferation is present, it may be advisable to administer the most promising chemotherapeutic agents by arterial routes leading to the neoplasm in order to afford higher concentrations in the blood leading to the involved area. Whether any of the chemotherapeutic agents will affect the tumor proportionately to their concentration remains to be determined. Furthermore, the length of time the therapeutic agent is kept in contact with the lesion is obviously of considerable importance. Substances that are removed promptly in the lesions, or that expend their effect rapidly (e.g., nitrogen mustard and short-lived radioisotopes), or that directly affect the capillary bed of the tumor (such as bacterial polysaccharides) offer desirable approaches. Methods to slow the venous return or enhance the afferent flow may further exploit this suggestion for therapy.

The data obtained demonstrate the necessity of determining the presence and amount of afferent supply to the lesions to be treated. Previous therapy by irradiation, nitrogen mustard, triethylmelamine and bacterial polysaccharides, at least in some instances, may reduce the arterial supply to cutaneous neoplasms. It is also likely that some cutaneous neoplasms will not possess an increased arterial blood supply. If intra-arterial therapy is contemplated, some measure of the vascularity of the lesion should be determined by dye, radioisotope, temperature or other suitable means. (J. Nat. Cancer Inst., April '51, H. R. Bierman, K. H. Kelly, K. S. Dod & R. L. Byron, Jr.)

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Studies With Gitalin (Amorphous) for the Treatment of Patients With Congestive Heart Failure

Gitalin, the water-soluble, amorphous mixture of glycosides extractable from Digitalis purpurea, was isolated by Kraft in 1912. Under the names of Gitalin-Kraft in Germany, Digisol in Holland, and verodigen in this country and abroad, this digitalis preparation had been subjected to considerable pharmacological, as well as clinical, investigation. It was the concensus that gitalin possessed many of the properties of digitalis leaf or digitoxin and that with appropriate dosage one could utilize gitalin wherever digitalization was indicated.

American investigators concluded that gitalin was just another digitalis preparation which could be used in place of those currently available. On the other hand, German investigators expressed the opinion that gitalin was superior to other digitalis preparations. The reasons for this were vague and reflected impressions rather than pharmacological or clinical data. In view of this divergence of opinion, the authors restudied this digitalis preparation. In this paper, their studies of amorphous gitalin for the treatment of congestive heart failure are presented in comparison with their previous experiences with other cardiac glycosides.

Gitalin was studied for its effectiveness in initiating and maintaining the digitalized state in 45 hospitalized and 46 ambulatory patients. The average therapeutic and toxic doses with rapid oral administration were 5.7 and 14.1 mg., respectively. The therapeutic ratio of 37 attained in patients digitalized rapidly is indicative of a greater therapeutic range than that of any other currently available digitalis preparation or glycoside. This greater therapeutic range and increased safety factor are also evident during slow digitalization and establishment of the maintenance dose. Thus, although toxicity noted with gitalin is similar in type and severity to that in other digitalis preparations, the likelihood of its occurrence with gitalin is less when initiating or maintaining the digitalized state because of its greater therapeutic range.

The aim in any therapy is to achieve the desired therapeutic effect without the occurrence of toxicity. With rare exceptions, a medication with clinical merit possesses both a therapeutic and a toxic dose. The safety of the medication may be thus expressed in terms of its therapeutic ratio or percentage of dose required for a desired therapeutic effect in terms of its toxic dose. The smaller the ratio, the greater the therapeutic range. The greater the therapeutic range, the more likely would a dose of the medication achieve clinical effectiveness without the occurrence of untoward reactions.

The most important advantage in the introduction of digitoxin, digoxin and lanatoside C has been their uniformity from lot to lot. However, in terms of more efficient or safer digitalization, these glycosides do not offer any advantage over digitalis leaf. Their therapeutic range is similar to the crude digitalis preparations. In the authors' experience, if a patient is no longer satisfactorily maintained with digitalis leaf and toxicity occurs with the next dosage level, the substitution of any of the above glycosides will result in the same response if comparable doses are used. The rapidity of dissipation and the factor of "completeness" of absorption do not overcome this inherent shortcoming of a narrow therapeutic range.

Because of the greater therapeutic range of gitalin, patients who previously required approximately two-thirds of the estimated or actual toxic dose to be digitalized or maintained now may achieve restoration of cardiac efficiency with approximately one-third of the toxic dose. The importance of this cannot be too strongly stressed. Since in any case, the attainment of the optimum therapeutic dose cannot be predicted in advance and must be reached cautiously by repeated doses, the use of a digitalis preparation with a greater therapeutic range has

definite advantages. The optimum therapeutic dose could be reached with a greater degree of safety and less likelihood of overshooting with the production of toxicity. Although the patient must be followed as carefully as before, the possibility of achieving a therapeutic effect before reaching a toxic level is greater for amorphous gitalin than for any other digitalis preparation. Cumulation is the same as in other digitalis preparations, but a greater amount of cumulation is required past the therapeutic effect to reach toxicity. It is also of interest to note that many physicians in the past preferred the infusion of digitalis which is an aqueous solution and, therefore, is essentially a solution of water-soluble glycosides or gitalin. Other desirable properties of amorphous gitalin include its rate of dissipation, uniformity in clinical potency from lot to lot and predictability of dosage. Amorphous gitalin satisfies the criteria demanded of a digitalis preparation to a greater extent than any other available glycoside or mixture of glycosides. It would appear, therefore, to be the digitalis preparation of choice for the treatment of the patient with congestive heart failure. (Am. Heart J., August '51, R. C. Batterman, A. C. DeGraff, L. B. Gutner, O. A. Rose & J. Lhowe)

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Terramycin Therapy for Meningitis

In recent years several antibiotic agents have been produced and their effectiveness tested in combating different kinds of meningitis; each has generally disclosed some disadvantage. Because of toxicity, streptomycin may cause impairment or even loss of hearing. Similar sequelae may result with dihydrostreptomycin, although it is less toxic. Some of the other antibiotics in general use may be responsible for nausea, vomiting or diarrhea. Certain antibiotics cannot be given intravenously and others should not be injected in the muscle because they are too irritating. From the standpoint of administration, penicillin is the only one that is ideal because it may be prescribed by any route. However, it is the authors' opinion that no remedy should be introduced into the thecal sac.

For some of these reasons, a clinical investigation of the value of terramycin in the therapy of meningitis was made. In the beginning, the plan was to select the first mild-appearing meningococcic meningitis patient admitted to hospital and start treatment with terramycin exclusively. If there was not a satisfactory response within 24 hours, it was proposed that the customary sulfonamide program be instituted. Clinical response in the first case, however, was such that 14 consecutive patients with meningococcic meningitis were treated with terramycin exclusively. The ages ranged from 1 to 36 years. There were no deaths.

Seven of the patients had no lumbar punctures, but the diagnosis was proved in all 14 by laboratory procedures. Seven patients each had one spinal tap.

Every patient received the initial dose of terramycin intravenously. With a dilution of 1 cc. of 5 percent dextrose to each milligram of terramycin, thrombosis occurred but once among 10 patients. The average number of days of

treatment was 7.6 and average total dosage of terramycin was 8.5 Gm. Although recovery often seemed to be complete within 6 days, the average hospital stay was 11.2. There were practically no unpleasant reactions from the drug.

These are believed to be the first meningitis patients treated exclusively with terramycin that have been reported. In addition, 3 patients with influenzal meningitis were treated successfully with a combination of terramycin and sulfadiazine. One of these patients admitted in a comatose condition and with a temperature of 105° F. made a spectacular recovery in a week's time. One patient with pneumococcic meningitis is now being treated and he has shown an excellent response to terramycin without other medication. (J. Pediat., August '51, A. L. Hoyne & E. R. Riff)

Note: Since the preparation of this paper, 9 additional patients have been treated exclusively with terramycin. Of these, 6 had pneumococcic meningitis; 5 recovered and 1 died of bilateral pneumonia. The 3 other patients each had Hemophilus influenzae meningitis and all recovered. Their ages were 4 months, 9 months and 3 years. (Authors' note)

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Effects of Streptomycin Upon the Human Fetus

On several occasions the administration of streptomycin to a pregnant woman was deemed necessary for treatment of tuberculosis. Molitor and coworkers have reported that weanling rats given repeated doses of streptomycin showed a retardation of growth and pronounced nervous hyperexcitability. No such changes were noted in adult rats. These observations suggest that the immature organism may be more susceptible to the neurotoxic effects of streptomycin than the adult. Since streptomycin crosses the placenta, the possibility of fetal damage from prolonged administration of the drug required consideration. In the two clinical reports that have appeared, a total of 7 infants whose mothers received streptomycin during pregnancy were studied. The infants were followed for 2 to 11 months after birth. All were said to be normal. However, apparently not all the infants had their vestibular function tested.

Presented here are 3 additional cases in which the maternal indication for the use of streptomycin was considered sufficient to risk the theoretical chance of injury to the fetus. Prior to the birth of each infant, the mothers received streptomycin for periods randing from 23 to 40 days and in doses totaling 23 to 40 Gm., during mid and late pregnancy.

Careful neurologic examinations (including tests of vestibular function with the Barany turning technic) repeated upon the infants at frequent intervals up to 1 1/2 years following delivery revealed no evidence of damage from the drug. Although 2 of the infants were born prematurely (cause unknown), their general development is normal to date. While this limited experience fails to prove that the fetus is safe from the possible neurotoxic effect of streptomycin

when the mother receives the drug, it suggests that such is the case. (A. M. A. Am. J. Dis. Child., July '51, A. Rubin, J. Winston & M. L. Rutledge)

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The Overweight Child

The proper appraisal of normal weight includes relation to age, sex, height, and, very importantly, body build. Body build includes mainly skeletal build and also muscle build. If Pryor's or Stuart's tables are used as weight standards, body build is taken into consideration and a more correct normal weight figure is obtained. Woods-Baldwin tables may not properly cover the body factor. Those children are considered obese and in need of treatment who are 20 percent or more over this ideal weight figure.

Weight reduction should be started in obese children of 6 years or older. Treatment includes diet, psychotherapy, drugs, exercise and efforts to raise the basal metabolic rate in about that order of importance. Psychotherapy is helpful for controlling excessive appetite, but it is difficult to carry out.

The first step in therapy is to convince the child that he should reduce. The physician can give only advice and directions; the patient must be willing. While a child can be convinced, he must have confidence in his physician, and the physician must relay confidence in his treatment of obesity to his patient.

Weight reduction of a child should be carried out gradually over a long period of time to avoid too great a metabolic disturbance, and to cause a minimal disturbance of the normal growth processes. The loss in the first 4 to 6 weeks will be greater than later; each week a 1 or 2 pound loss will be satisfactory. Diet is the most important part of therapy.

The reduction in caloric intake should be gradual. It is very hard on any overeater to be cut down suddenly to nearly basal caloric intake; the procedure easily disheartens a child. It is helpful but not always possible to obtain a full list of the child's habitual caloric intake for about 1 week as a take-off point for cutting down. From this point the dietary intake can be gradually cut by 250 calorie steps every 3 to 5 days until a desired caloric intake is reached (computed from tables given).

About one-quarter of obese patients will lose satisfactorily on this qualitative reduction diet. The average child between the ages of 6 and 16 using the diet, daily taking 3 meals of average servings and using some of the listed fruits and vegetables as fillers between meals, will ingest about 1,600 to 2,500 calories daily.

It has been the author's experience that most obese patients lose better on a quantitative diet. As it is more precise, it often impresses them with the need to stay on it and there are fewer chances for infractions. Usually a child eating about 4,000 calories daily, who needs only 3,000 to 3,500 between 12 and 16 years, can be put on 2,500 calories as the qualitative diet, and then, if not losing, stepped down within a week to the quantitative 2,200 calorie intake. There has usually been no great trouble keeping adolescent children on these diets

down to 1,200 calories. The diets are filling, due principally to the quantity of vegetables and lesser portion of the fruit. The calorie intake is lowered to a point where weight loss of 1 to 2 pounds weekly occurs. The loss in the first 4 to 6 weeks is sometimes quite marked and less so thereafter; if the weight remains stationary for more than 3 or 4 weeks, then the next lower calorie intake is given.

For adolescents, 1,200 or 1,000 calories (very near basal) is the lowest intake commonly needed; 1,500 calories commonly produces satisfactory weight loss; it is rare that the 800-calorie diet must be used. As a rule the author does not go below basal requirements. Such semistarvation naturally should not be permitted for more than several weeks. It is possible to maintain such low-calorie intake with appetite reducing drugs.

The following suggestions have been helpful in obese infants and children up to 6 years of age: skim cow's milk up to 32 ounces daily, with only 5 percent carbohydrate addition; water feedings between mother's nursings: 3 and 5 percent vegetables and only 5 percent fruits and small portions of 10 percent fruits; bread, toast or crackers up to 3 slices daily with very little butter or oleomargarine; cereals served without cream or sugar but with some of the allotted skim milk and saccharine; lean meats; an egg daily; all servings to be average single ones; fillers; daily extra vitamins as concentrates and 1 Gm. dicalcium phosphate.

The various diets are adequate in protein for growth and development; they are quite well balanced; they are bulky enough for satiation; they are attractive in taste and not too monotonous because of the list of substitutions. The substitutions allow the adolescents to attend parties or eat at the school cafeteria. All of the food does not have to be eaten at a meal. On the 1,500 and 1,800 calorie diets some of the vegetables, or other foods, on the diet are fillers and can be eaten after school or before retiring at night. This is helpful, for many of these children are very hungry at these times.

Liquid restriction is worth-while if there has been too much intake. Each of the measured diets calls for at least 21 ounces of liquid as such, in the form of milk. This can be supplemented by noncalorie liquids up to minimum fluid requirements. Often patients will lose appreciably in the early weeks of reducing if excessive fluid intake is cut to normal. Excessive salt intake tends to excessive fluid intake, so that it is well to restrict sodium chloride additions to food. Food can be cooked with an ordinary amount of salt and seasoning. Nonlithiated salt substitutes (Neocurtisal) can be given to satisfy a salt appetite.

Drugs, Psychotherapy, and Exercise. Drugs are used only in conjunction with diet and exercise. Drugs inducing anorexia or raising the basal metabolic rate are necessary usually in about half of the patients. They should be used only as an aid when it has been demonstrated that adequate calorie restriction has not reduced weight satisfactorily.

Thyroid has its greatest effect due to its calorigenic action and not because the patient lacks much of this hormone. He may have some hypothyroidism but not much, and this is secondary. Great doses often are necessary before the desired effect is obtained.

Propadrine hydrochloride, d-desoxyephedrine hydrochloride, d-amphetamine, and benzedrine are given in that order of preference. The first two are less likely to induce nervousness or insomnia. A small dose of these may induce marked anorexia which worries both the patient and the physician. Give at the start 5 mg. doses before breakfast and mid-afternoon, and increase by a 5 mg. dose once daily every 3 to 4 days until hunger disappears. Occasionally children will be too nervous or will not sleep well when taking amphetamine, but this is rarely the case with propadrine. Often, drugs can be stopped as the patient loses sufficient weight, or the drugs can be used intermittently if weight loss is satisfactory or if too many adverse complaints occur. Some patients rapidly become tolerant, especially to amphetamine.

The author has had limited experience with psychotherapy, which has not yielded as good results as diet alone. Close questioning of patients and families has not yielded much indication of a psychoneurosis in an obese child. Some families eat more than needed without realizing this excess. Also, obese adolescent girls often are selfconscious about their condition, and may stay by themselves, or be left out of some activities by their contemporaries. They thus lead sedentary, lonely lives, eating for diversion and pleasure, or by habit. One should point out the disadvantages of poor appearance, possible ill health (diabetes in later life, etc.), and urge activity and association with others, appealing to a sense of pride and self-confidence. Psychotherapy needs further use and exploration in the case of the obese, and it should prove helpful.

Exercise is in order in all cases except when contraindicated, as in active Legg-Perthes disease, advanced heart disease, and like conditions. The more prolonged and vigorous the exercise the better; the child should exercise until perspiring for at least some time.

Prognosis. Nature will "cure" only about one-third of obese children; this change is likely to occur with puberty. But it is a mistake to expect this physiologic correction or to wait for it. The results have been obtained with diet, exercise and drugs combined. About 75 percent of patients so treated attained fairly normal weight in about 3 to 6 months. The reduction diet is continued until the patient is at the ideal normal weight, or no more than 10 percent above this poundage. (GP, August '51, W. A. Reilly)

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Tumors of Childhood: Surgeon's Viewpoint

American Cancer Society statistics for Oregon (1946) show that childhood cancer was exceeded as a cause of death only by accidents. During a 3 year period from 1946 to 1949, 175 tumor cases were admitted to the Doernbecher Memorial Hospital for Children, representing more than 2.5 percent of the total number of hospital admissions.

The high mortality of proved malignancies of childhood and the demonstration in recent years that the operative risk of major surgical procedures is not excessive suggest that a more radical surgical approach to the problem of the

malignancies of childhood is warranted. Furthermore, on the basis of their experience with unexpected long-time survivals of children having apparently inoperable or incompletely removed malignant tumors, as well as the biologic unpredictability of pediatric tumors based on histologic study, the authors find that a liberalization of the indications for cancerocidal x-radiation seems justified.

The clinically malignant nature of some benign tumors and the possibility of malignant change in others indicate the advisability of prophylactic removal of the so-called "dangerous lesions of childhood". A selected and important group of these lesions are presented:

Skin. The clinical significance and close relationship between the so-called junctional nevus and melanoma has been stated by Allen in a classical study. It is recognized that the junctional nevus develops, with adolescence, a high degree of malignant potential. The flat or elevated brown nevus of the skin which is situated below the level of the umbilicus, on the palmar surface of the hand, or the plantar aspect of the foot is a dangerous lesion at any age. It should be excised before the age of puberty. A pigmented lesion in any location which demonstrates color change, accelerated growth, stinging, burning or itching sensations may be undergoing malignant transformation. These findings are indications for a wide surgical removal of the lesion. Cavernous hemangioma and hemangioendothelioma show a tendency to infiltrate tissues and extend locally. The complications of ulceration and hemorrhage are not uncommon. The possibility of complete spontaneous regression of these vascular tumors is unlikely and their proper treatment is a problem for the surgeon, the radiologist and the dermatologist.

Nerve Sheath Tumors. The neurilemmoma (palisade-sheath tumors, perineural fibroblastoma, schwannoma) and neurofibromatosis (von Recklinghausen's disease) should be considered as premalignant tumors. The incidence of malignant change in these lesions is higher than generally realized. In one series of 40 patients with neurofibromatosis, 9 died of neurogenic sarcoma, an incidence of malignancy of more than 22 percent. It would seem a worth-while precaution to remove all solitary nerve sheath tumors, those of more than 1.5 cm. in diameter, and lesions which show a tendency to enlarge with associated neurologic symptoms.

Connective Tissue Tumors. Lipoma, lipomatosis, fibroma, lipofibroma, chondroma and osteochondroma are benign tumors which may undergo a transition to sarcoma. It is well to guard against this possibility by removing solitary chondromas and other connective tissue neoplasms, particularly if the tumor is bulky, gives rise to subjective symptoms or if it is subject to trauma.

Embryonal Tumors. The dermoid cyst and teratoma assume an important place in any discussion of premalignant lesions of childhood. The more complex the structure of the tumor, the more likely the possibility of malignancy. A diagnosis of benignancy is always made with considerable reservation, even after the most careful histologic study of the tumor. The complex teratoma should be considered as a tumor which possesses a high malignant potential or is actually

malignant. Proper treatment is by surgical excision. The prognosis depends upon the patient's survival of the operation and should be made with caution.

Masses of the Head and Neck. The early diagnosis of retinoblastoma can be made in about one-half of the cases by routine postnatal ophthalmoscopic examination, according to Gaisford. The solitary adenoma of the thyroid gland is more likely to be malignant in the child than in the adult, and its discovery is an indication for its removal. Branchiogenic cysts and sinuses and teratomatous masses in the neck should be excised.

Mediastinal Tumors. The problem of the asymptomatic mediastinal tumor assumes increasing importance with the introduction of mass survey chest x-ray examinations. The most common tumors encountered are the neurofibroma, ganglioneuroma, dermoid cyst and teratoma. The mediastinum should be considered as a critical anatomic area. The specific tumor that will degenerate, perforate or cause extensive destruction of vital structures by pressure and local invasion cannot be predicted. Moreover, it is estimated that at least 10 percent of benign mediastinal tumors will undergo malignant transformation. Exploratory thoracotomy and surgical removal are indicated.

Tumors of the Abdomen. In the very young, neuroblastoma and Wilms's tumor are most frequent. Exploratory laparotomy should follow the discovery of an abdominal mass with a minimum of delay. Traumatic manipulative procedures in the preoperative period are to be discouraged and extensive investigative studies are usually not indicated. It is not the authors' policy to recommend preoperative x-radiation for neuroblastoma or Wilms's tumor.

Adenomatous Polyps. Helwig has discussed the evolution of adenomas of the large intestine and their relation to carcinoma. Swinton and Warren were able to demonstrate a histologic transition from normal mucosa to adenocarcinoma in 14 percent of all their cases of carcinoma of the colon and rectum, and they estimated that a much higher percentage of malignant change in the colon and rectum than this arises in previously benign polypoid tumors. The premalignant nature of adenomatous polyps is especially striking in the case of congenital polyposis of the colon.

Ectopic Testis. The chance of malignant change developing in the undescended testicle is increased approximately 50 times over this chance in the normally situated testis. The inguinal or abdominally placed testicle is a real cancer hazard in the adult. The ectopic testis should be removed if it cannot be placed in the scrotal sac by appropriate surgical technics.

Penile Carcinoma. Wolbarst has stated that circumcision of every male child in infancy would virtually eliminate the possibility of penile carcinoma. (Surgery, August '51, C. G. Peterson & G. Gilmer, Jr.)

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Amithiozone Treatment of Pulmonary Tuberculosis

The treatment of tuberculosis with a new agent, 4-acetylaminobenzaldehyde thiosemicarbazone (amithiozone), was first investigated in Germany prior to 1948.

A survey by Hinshaw and McDermott of approximately 2,000 patients so treated led to the recommendation that the drug be evaluated in this country. (See Medical News Letter, Vol. 15, No. 4, 24 February 1950.)

The present study, a part of the investigative program of the Veterans Administration, was undertaken to test the therapeutic effect of amithiozone alone, and in combination with streptomycin, on the course of pulmonary tuberculosis in a group of hospitalized patients. The sensitivity toward both amithiozone and streptomycin of the strains of M. tuberculosis isolated from the patients was determined before, during and after the course of therapy.

Methods of Study. Selection of Patients. Following an observation period of 1 month or longer, 21 male patients were chosen whose pulmonary tuberculosis was proved by demonstration of M. tuberculosis in the sputum or gastric washings and whose disease roentgenographically had shown no improvement or had become worse. At the time treatment was begun, 5 of the patients had moderately advanced disease and 16 had far advanced disease. According to roentgenographic interpretation, 3 patients had predominantly exudative lesions, 2 predominantly productive and the remaining 16 mixed exudative-productive lesions. Pulmonary cavitation was present in 16 patients, with a single cavity in 7 and multiple cavities in 9.

Regimen of Treatment. The method of administration and the dosage of each drug were those recommended by the Committee on Therapeutic Agents of the Veterans Administration. Ten patients received amithiozone alone. The initial dose was 50 mg. given orally each day during the first week. The dose was then increased by 50 mg. weekly until a dose of 200 mg. per day was reached by the beginning of the fourth week. This dose was continued until 120 days of therapy had been completed. Thus, each patient who completed a course of treatment received 14.7 Gm. of amithiozone.

Eleven patients, chosen alternately, were given combined treatment: amithiozone, as outlined above and, in addition, streptomycin, 1 Gm. daily in one intramuscular injection during the entire period of treatment.

Comment. In each patient the roentgenographic and clinical features of the disease were clear cut so that any change induced as the result of treatment could be detected and evaluated. Although the number of patients studied is small, certain trends are evident.

Patients treated with amithiozone alone failed to show consistent improvement by roentgenographic criteria; they did not gain weight, the amount of sputum did not decrease, decline in fever was not constant and subjective feeling of well being was lacking. On the other hand, patients treated with the combined amithiozone and streptomycin therapy showed unmistakable evidence of improvement in these aspects. It is uncertain, however, whether similar results might not have been obtained by the use of streptomycin alone.

Untoward effects from amithiozone were encountered in both groups, but usually disappeared rapidly after the therapy was discontinued.

It was shown that strains of M. tuberculosis resistant to amithiozone developed in patients treated with this drug alone. On the other hand, no resistant

organisms developed in those patients to whom amithiozone and streptomycin were given concurrently. The number of patients studied is too small, however, to provide proof that the combined therapy can prevent the emergence of strains of M. tuberculosis resistant to either drug. (Am. Rev. Tuberc., August '51, H. S. Sandhaus, D. E. Jenkins, K. L. Burdon & Béla Halpert)

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Lung Function Studies in Poudrage Treatment of Recurrent Spontaneous Pneumothorax

It is now generally recognized that recurrent spontaneous pneumothorax of nontuberculous origin is best handled surgically. Several forms of treatment are available, but exploratory thoracotomy, resection of the pulmonary cysts, blebs or bullae, with or without additional talcum powder poudrage to induce pleuritis, seems to be the preferred method of treatment. The use of talc to induce pleural symphysis has been criticized because of its supposed damage to lung function, and the purpose of this paper is to report on lung function studies in recurrent spontaneous pneumothorax treated by this method.

Thirty patients have undergone exploratory thoracotomy and talcum powder poudrage in the treatment of recurrent spontaneous pneumothorax. Pulmonary function studies were accomplished on 4 patients, one of whom had surgery performed on both sides.

In Case 1 the vital capacity fell 3 percent after the poudrage. The relative vital capacity of the left lung fell 2 percent, the relative minute ventilation of the left lung fell 6 percent and the percent oxygen consumption of the left side rose 5 percent. These changes do not seem significant.

In Case 2 the vital capacity fell 13 percent after the bilateral operation. After the left operation alone, the relative vital capacity of the left lung rose 2 percent, the relative minute ventilation of the left lung fell 7 percent and the percent oxygen consumption of the left side fell 4 percent. None of these changes seem to be significant. After the second operation on the right side, the relative vital capacity of the right lung fell 7 percent, the relative minute ventilation of the right lung rose 11 percent and the percent oxygen consumption of the right side fell 30 percent. The fall in percent oxygen consumption on the right side after the right poudrage seems significant.

In Case 3 the vital capacity fell 13 percent after the poudrage. The relative vital capacity of the left lung rose 8 percent, the relative minute ventilation of the left lung rose 6 percent and the percent oxygen consumption of the left side rose 29 percent. This increase in oxygen consumption on the left side seems to be significant.

In Case 4 the vital capacity fell 3 percent after the poudrage. The relative vital capacity of the left lung rose 1 percent, the relative minute ventilation of the left lung rose 19 percent and the percent oxygen consumption of the left side was unchanged. This increase in minute ventilation on the left side seems signicant.

Open thoracotomy and talcum powder poudrage for recurrent spontaneous pneumothorax produced no consistent decrease in pulmonary function as determined by bronchospirometry in the 4 patients. The observed changes in pulmonary function do not seem to be of greater degree than would be expected to follow any open thoracotomy. The authors conclude that the introduction of talcum powder to induce pleural symphysis had no demonstrable harmful effects during the period of their observation. (J. Thoracic Surg., July '51, Lt. Col. J. S. Paul, MC, USA, E. J. Beattie, Jr. & B. Blades)

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Use and Abuse of the Dextrose Tolerance Test

Statements in the literature concerning carbohydrate metabolism are usually based on the dextrose tolerance test (otherwise called the glucose tolerance test or the sugar tolerance test). The test dose of sugar in these cases is usually from 50 to 100 Gm. given by mouth. When the dextrose tolerance curve is diabetic in type, the conclusion reached is, "The dextrose tolerance test indicated a deficiency in the oxidation of carbohydrate." Such statements are a misinterpretation of the nature and significance of the dextrose tolerance test and indicate a lack of awareness of recent developments in the field of carbohydrate metabolism.

The author presents evidence to show that the dextrose tolerance test is chiefly an index of the efficiency of blood sugar regulation. Although increased sugar utilization and the storage of glycogen do play minor roles in determining the shape of the dextrose tolerance curve, the most important factor is the efficiency of a regulating mechanism which resides chiefly in the liver. The dextrose tolerance test, when properly done, gives information concerning the function of the liver.

There is a very efficient blood sugar regulating mechanism in man and in the higher mammals. Whether the degree of activity be large or small, the blood sugar level remains practically constant, even though there is a tremendous difference in the rate of utilization of carbohydrate. When a muscle is put from complete rest into violent activity, its oxygen consumption can be increased some 30 times, yet the blood sugar level remains fairly constant except during the most violent and prolonged work. Similarly, whether an individual is fasting or eating a hearty meal, the blood sugar stays constant. The blood sugar level can be disturbed for only 1 or 2 hours after taking in an amount of sugar sufficient to last for 6 to 12 hours. Obviously, all that sugar is not oxidized within 1 or 2 hours; part is used and part is stored. There is, then, an additional and efficient regulating system which disposes of that sugar rapidly and brings the blood sugar back to its former level. The 3 factors operating in the disposal of the sugar given in the dextrose tolerance test are (1) hepatic regulation, (2) increased utilization and (3) increased glycogen storage. Of these, hepatic regulation is the most important factor; the others are minor.

When the dextrose tolerance test is done by giving the test dose of sugar by mouth, the shape and significance of the dextrose tolerance curve are obscured by variations in the rate of absorption of the administered sugar from the gastrointestinal tract. The curves are very variable, even in the same normal individual repeated at different times. A slight fear of the procedure, or a little nausea from the lemonade made up for the test, may be sufficient to delay absorption from the gastrointestinal tract and give a flat curve which completely obscures the significance of the test.

The author believes that the oral dextrose tolerance test as ordinarily used and interpreted is practically worthless. While it will give a diabetic type of curve in a moderate-to-severe diabetic, a simple fasting blood sugar level will give as much information. In the milder diabetics, the curve is so variable that it is not worth doing. In order to avoid the variable factor of intestinal absorption, intravenous test is preferred. The author gives 1/3 Gm. of glucose per Kg. of body weight in 50 percent solution (that is, just as it comes from the ampule) intravenously, and injects that amount within 3 to 5 minutes.

On the average, in such tests, the normal curve is back to its original pre-test level within 60 minutes. The diabetic curve (mild) is not back within 120 minutes, and the average diabetic curve is not back even within 180 minutes. The curve of liver disease takes more than 60 minutes and less than 120 minutes. These curves are based on the mildest cases of diabetes and liver disease, respectively, that the author could find and clinically diagnose and corroborate with laboratory tests. Thus, with the intravenous dextrose tolerance test, one can distinguish between even the mildest diabetes and the mildest liver disease.

The initial blood sugar level for either diabetes or liver disease may be either normal or definitely elevated. The differential diagnosis depends on the curve, i.e., the length of time which it takes for the blood sugar mg. percent to return to its pre-test level. It is a matter of some importance to distinguish between mild liver disease and diabetes, because if a patient with liver disease is treated with restricted carbohydrates and insulin, he may be made worse. The author believes that there are many patients under long-continued treatment for diabetes who had liver disease to begin with. On the other hand, if patients with a little sugar in the urine and a moderately elevated blood sugar level are watched for and diagnosed as cases of liver disease and so treated, they will become quite symptom-free. (Postgrad. Med., Aug. 1951, S. Soskin)

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Armed Forces Blood Donor Program

The Department of Defense is planning a concerted effort to replenish its gravely depleted supply of human blood plasma.

The depletion of the Armed Forces' plasma reserve is due primarily to the extensive use of plasma in Korea, where its use in forward areas had kept many of the wounded alive until they could be evacuated to an area where whole blood was available. The use of plasma and whole blood in Korea is a major factor in the reduction of the mortality rate among wounded. The decline in this rate is most easily expressed in the number of men per hundred who died after reaching the most forward surgical hospital. In World War I, 8 to 11 per 100 died. In World War II, the number was reduced to 4.5 and in the Korean conflict it is 2.6 men per hundred.

Field installations of the Army, Navy, Air Force and Marine Corps have been instructed to cooperate with the Red Cross to the fullest possible extent to raise the level of available plasma reserves. All commands have been directed to wage a continuous and vigorous campaign in conjunction with the Red Cross, to persuade the civilian and military population to contribute whole blood to the Armed Forces. The military services are also establishing an Armed Forces blood donor program within the framework of the overall campaign, the primary purpose of which is to obtain blood from service personnel and civilian employees on military bases within the continental United States.

The value of a reserve supply of plasma has been proved in Korea, yet it is one vital commodity that assembly lines cannot produce and money cannot buy. To assure each soldier, sailor, airman and Marine an adequate reserve of this vital fluid for use when and where he needs it, the Department of Defense has financed the expansion of blood processing laboratories, and asked the Red Cross to collect for the Defense Department nearly 3 million pints of whole blood to be processed into more than a million plasma units between July 1, 1951 and July 1, 1952.

Ups and downs in the Korean campaign have had a noticeable effect on the amount of whole blood the Red Cross collected. When the going has been tough in Korea, collections have been good. Conversely, when the United Nations has had the upper hand, collections have been well below normal. Indicative of this is the fact that since the Kaesong ceasefire negotiations began collections have dropped to one third of the requirement.

Blood processing laboratory capacity has been expanded and will be capable of handling more than 280,000 pints monthly by January 1952. In the past few months collections have averaged 35,000 to 40,000 pints monthly.

Collection of blood in the case of military installations will be handled by military installations themselves when they are geographically separated from a regular Red Cross collecting agency or a cooperating blood bank, or it is impracticable to use these facilities. Civilians may contribute their blood through either Red Cross Defense Blood Centers, Red Cross Regional Centers, or cooperating private blood banks, or through the military program if they are civilian employees.

To assure that the 2,800,000 pint quota for the fiscal year is met, the monthly quotas for the remainder of the fiscal year will be raised to 300,000 pints. (PIO, Dept. of Defense)

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Attention Personnel Officers

In order to record as much information as possible concerning special qualifications of personnel of the Hospital Corps, the cooperation of all ships and stations is requested. To accomplish this task, use the appropriate lines of the NavMed HC-3 card:

Line 9 - All designated NJC code numbers.

Line 10 - Any qualification or skill not covered by a designated NJC code number. Show years of education, high school graduate, degrees conferred, licensures, certificates of formal courses of study or apprenticeships, etc.

Line 14 - Any further remarks concerning qualifications or special achievements, commendations, meritorious awards, meritorious mast, correspondence courses completed, USAFI educational level tests, etc.

The prompt submission of NavMed HC-3 cards on Hospital Corps personnel has been overlooked in numerous instances. It is hoped that the use of discrepancy reports by the Bureau of Medicine and Surgery to call the activities' attention to the failure to submit NavMed HC-3 cards promptly in accordance with Article 23-6, Manual of the Medical Department, will not be necessary. (Personnel Div., BuMed)

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Where Are The Recruiters?

HMC's and HM1's desiring recruiting duty should submit their requests in accordance with Article C-5208, BuPers Manual. Eligibility is governed by the length of sea duty on current tour. Assignment to shore duty other than recruiting service automatically removes an individual's name from the recruiting eligibility list. It is, therefore, necessary to resubmit your request for recruiting duty on a subsequent tour of sea duty if that assignment is still desired. Requests from the above mentioned rates who are now serving at sea are desired. Do not reference this publication when requesting this duty. (Personnel Div., BuMed)

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Applications From Reserve LT and LTJG Dentists for Appointment in Regular Navy Dental Corps

Applications are being accepted from Reserve dental officers for appointment in the Dental Corps, U. S. Navy. Such officers may be serving on active or inactive duty in the grades of lieutenants or lieutenants (junior grade), but must be under 37 years of age. Reserve dentists on inactive duty must have had previous military experience other than training duty to apply. (Volunteer applications are also sought from 189 "Priority I" dentists for commission in the Naval Reserve and immediate active duty.)

No professional examination is required. The age and professional experience of the applicants selected will determine the grade of appointment. Normally the grade will be the same as that held in the Naval Reserve, but will not necessarily be with the same precedence and date of rank.

Applicants on active duty should submit letter requests for consideration to the Chief of Naval Personnel via their commanding officer. A special Fitness Report, two copies of the Report of Medical Examination and a Report of Medical History should accompany the application. All of these requests should be received in the Bureau of Naval Personnel prior to October 15, 1951.

Applicants on inactive duty should apply at their nearest Navy Recruiting Station and Office of Naval Officer Procurement. (PIO, BuPers)

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Microbiological Institute Research Grants

Various "new drugs" used in the treatment of tuberculosis will be evaluated under more than a dozen of the grants awarded by the Microbiological Institute of the National Institutes of Health. These grants are among a total of 102 grants amounting to $1,088,952 which were awarded to non-Federal medical scientists by the National Microbiological Institute.

A large number of these grants are concerned with diseases other than tuberculosis. Investigators will variously attempt to determine whether birds, as well as mosquitoes, are carriers of the virus which causes encephalitis; whether DDS (diamino diphenyl sulfone) is as effective in the treatment of leprosy as are other, more expensive sulfones; and what new drugs may be developed for the treatment of amebiasis and schistosomiasis which would be as effective as emetine but considerably less toxic. Other studies will be made on malaria, Q-fever, meningitis, several fungus diseases and on basic problems of the growth mechanism and action of bacteria and viruses.

Because tuberculosis tends to relapse, several investigators will continue to observe for a period of years those patients who have recently responded to chemotherapy. They will determine the frequency and severity of relapse in different types of tuberculosis treated with different compounds. They will also evaluate certain ill effects caused by drugs, such as decrease in hearing, which

sometimes occur long after initial treatments. Studies will be also made of the resistance of tubercle bacilli to antituberculosis agents which seem effective in early stages of treatment but whose continued use has frequently been disappointing. (News Release, Federal Security Agency, Public Health Service, National Institutes of Health)

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List of Recent Reports Issued by Naval Medical Research Activities

Naval Medical Research Institute, NNMC, Bethesda, Maryland

Attempts to Transmit Haemoproteus Columbae by Means of Mosquitoes, NM 000 018.07.03, 12 March 1951.

Effects of Ionizing Radiation on Oral Structures. I. Pilot Studies on Dental Caries in the White Rat, NM 006 012.04.35, 19 March 1951.

Photographic Method of Recording Areas of Inhibition and Zones of Hemolysis in Seeded Agar Plates, NM 000 018.07.05, 7 June 1951.

Reproduction of Printed Patterns by Vacuum Evaporation, NM 000 018.07.08, 14 June 1951

Light Scattering Studies on Actin, NM 000 018.07.07, 15 June 1951.

Note on the Physical Adsorption of Gases in Capillaries and on Small Particles (Nucleation of Condensation), NM 000 018.06.06, 15 June 1951.

Medical Research Laboratory, U. S. Naval Submarine Base, New London, Conn.

An Ophthalmological Study of Visual Acuity Under Dim Illumination, MRL Report No. 173, NM 003 041.04.04, 6 June 1951.

U. S. Naval School of Aviation Medicine, USNAS, Pensacola, Florida

Radial Acceleration and the Urinary Output of Supinated Man, NM 001 059. 02.08 (formerly NM 001 010), 18 April 1951.

A Composite Sensory Projection Area in the Cerebral Cortex of the Cat, NM 001 066.01.01, 15 June 1951.

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From the Note Book

1. On 15 August 1951 the new addition to the U. S. Naval Hospital, St. Albans, New York, was dedicated. Rear Admiral Lamont Pugh, the Surgeon General, delivered the principal address. The new addition has 20 wards, administration building and a radiological unit. (PIO, BuMed, 15 Aug. 1951)

2. In an effort to curb the unnecessary toll caused by cancer of the cervix, grants to 6 institutions have been made by the National Cancer Institute of the National Institutes of Health. Cervical cancer will be considered from several approaches such as, (1) the relationship of this type of cancer to race, marriage, diet, customs and other factors; (2) the screening of 20,000 women over the age of 19 in an effort to determine the incidence rate and way of control in a normal population; (3) the relationship of pregnancy to cervical cancer; (4) studies of preinvasive cervical cancer. (PIO release, FSA, PHS, NIH, 15 Aug. 1951)

3. Dramamine appears to be of value in treating vestibular disturbances complicating arteriosclerotic and hypertensive cardiovascular disease. (Am. Heart J., Aug. 1951, I. R. Goldman, N. S. Stern & T. N. Stern)

4. Ocular tension has been followed at 2 hour intervals over 24 hours in 34 cases of glaucoma simplex. The curves obtained are discussed in relation to visual field defects, blood pressure, body posture, provocative tests, ingestion of food and other clinical tests. (Brit. J. Ophth., Aug. 1951, D. Langley & H. Swanjung)

5. A discussion of upper respiratory infection as a factor influencing susceptibility to poliomyelitis will be found in the New England Journal of Medicine, 9 August 1951, by T. H. Ingalls and W. L. Aycock.

6. At Frankfurt, Germany, for the first time a hospital epidemic of Q fever could be definitely traced to a human carrier. The authors believe that a patient suffering from Q fever is not always and necessarily a source of infection. (R. Siegert, Simrock & Stroder, quoted in Trop. Med. & Hyg., July 1951)

7. The description of an outbreak of Q Fever in Sokol, Yugoslavia, appears in Public Health Reports, 10 August 1951. (E. S. Murray, P. Djakovic, F. Ljupsa & J. C. Snyder)

8. During 1950 the Mayo Clinic examined 96 patients who had apparently been cured of microscopically proved cancer and who had received radium therapy with supplementary roentgen ray treatment at least 5 years previously. Of the 96 patients, 74 had received no treatment for 5 years, 20 none for more than 10 years and 2 none for more than 20 years; 81 of the 96 had been treated for cancer of the uterine cervix. (Proc. Staff Meet. Mayo Clin., 1 Aug. 1951, R. E. Fricke & M. Van Herik)

9. The 10th semiannual report of the Atomic Energy Commission shows 28 million dollars spent on biological and medical research and equipment. (Miscellany, J. A. M. A., 11 August 1951)

10. "Heroin Addiction in Adolescent Boys" is discussed in the Journal of Nervous and Mental Disease, July 1951. (P. Zimmering, J. Toolan, R. Safrin & S. B. Wortis)

11. A study of the familial incidence of disseminated sclerosis and its significance appears in Brain, June 1951, by R. T. C. Pratt, N. D. Compston and D. McAlpine.

12. The most powerful atom smasher known to the world is a 450,000,000 electron volt synchrocyclotron recently dedicated at the University of Chicago. (Science News Letter, 11 Aug. 1951)

13. A method for collecting specimens for cytologic study of tubal malignancy is described in Science, 17 August 1951 by K. S. Maclean.

14. Examples from the therapeutic spectrum of cortisone are shown in Postgraduate Medicine, August 1951, by A. Gibson, C. E. Lyght, S. Fromer and L. P. Strean.

15. The National Safety Council reports that the 6 months highway death toll for 1951 is 16,220 -- 1,200 deaths or 8 percent above the same period of 1950. If this trend continues, the 1951 traffic death toll will be 37,800, almost 3,000 above last year and the 4th highest traffic toll in history. (Medical News, J. A. M. A., 11 Aug. 1951)

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A. Lawrence Abel, M. S., F. R. C. S., in an article, "Pitfalls of Planning" appearing in the British Medical Journal (Supplement) of 4 August 1951, quotes the following words of Abraham Lincoln:

You cannot bring about prosperity by discouraging thrift.
You cannot strengthen the weak by weakening the strong.
You cannot help the wage-earner by pulling down the wage-payer.
You cannot further the brotherhood of man by encouraging class hatred.
You cannot help the poor by destroying the rich.
You cannot establish sound security on borrowed money.
You cannot keep out of trouble by spending more than you earn.
You cannot build character and courage by taking away men's initiative and independence.
You cannot help men permanently by doing for them what they should do for themselves.

JOINT LETTER

BUMED CIRCULAR LETTER 51-115 8 August 1951

From: Chief, Bureau of Medicine and Surgery
Chief of Naval Personnel

To: All Shore Stations

Subj: Physical Fitness of Naval Reservists, Officer and Enlisted, for orders to extended active service

Ref: (a) Par. 2118, ManMedDept, 1945
(b) Par. 2118.2, ManMedDept, 1945
(c) Par. 2118.3, ManMedDept, 1945
(d) ALSTACON 201948Z of 20 Jul 1950
(e) Joint BUMED-BUPERS Ltr (BUMED Cir Ltr No. 51-77); NDB 15 May 1951, 51-359, p 42

1. Reference (e) is hereby canceled and superseded.

2. It is noted that many Naval Reserve officer and enlisted personnel are being accepted by medical officers in the field as physically qualified for extended active service, with or without conditional waivers, even though they cannot reasonably be expected to perform unlimited active service. The need at present is for Reserve personnel who can perform duty at sea or on foreign shore for a normal tour. Those who require major surgical treatment or who are likely to need extensive medical study or treatment are to be considered not physically qualified for active military service pending review of the records in each case in the Navy Department.

3. Naval Reservists in reporting for extended active duty are required to meet the same physical standards as other personnel of similar rank or rating who enter into active service (reference (a)). Personnel who do not meet the standards for original appointment or enlistment (reference (b) and (c)) are not to be accepted for extended active duty unless a conditional waiver is granted in accordance with the provisions of reference (d).

4. Reference (d) was promulgated for the purpose of expediting ordering into active service those reservists who are physically able to perform unlimited duty but who present defects or disabilities which require waiver for administrative reasons. The conditional waiver (reference (d)) is not to be recommended or granted in any case where the individual is:

a. unlikely to be able to perform unlimited duty

b. in need of further study of major nature (other than chest x-ray or serology testing)

c. in need of major surgical treatment (such as for hernia, hemorrhoids, varicose veins, etc.)

d. suffering from, or presents a bona-fide history of, such recurrent or progressive, and potentially disabling diseases as arthritis, malignancy, joint derangement (hip, knee, shoulder), asthma, bronchiectasis, pulmonary tuberculosis, (reinfection type), psychoneuroses or psychoses, hypertension, especially with diastolic pressure above 95 millimeters of mercury, peptic ulcer or ulcerative colitis.

5. In the case of those members where doubt exists as to physical fitness to perform unlimited extended active service, the medical examiners should disqualify the individual physically. However, in unusual circumstances where a waiver, contrary to the above, is believed in the best interest of the service, a dispatch should be sent to the Bureau of Naval Personnel with the Bureau of Medicine and Surgery and the prospective duty station as information addressees. The dispatch should list full name, rank or rate, serial or file and designator number, and state the nature and degree of disability with recommendation for approval of a waiver. Completed Forms 88 and 89 in all cases should be promptly forwarded to the Bureau of Medicine and Surgery.

6. In all cases where a substantiating physical examination is required (a pronounced change of physical condition or over 45 days elapses between physical examination and reporting date) to be conducted by the first naval activity reported to in compliance with active service orders, examining activity will not be limited by the above restrictions and will issue a conditional waiver for any additional defects requiring same if subject is considered reasonably able to perform the duties to which assigned. Where a change in physical condition results in subject not being considered fit for active service, orders will be so endorsed and unexecuted portion of orders will be automatically canceled. Provisions of paragraph 2 of active service orders apply.

C. J. Brown
Acting

L. T. Dubose

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BUMED CIRCULAR LETTER 51-116 8 August 1951

From: Chief, Bureau of Medicine and Surgery
To: All Naval Hospitals and Hospital Ships

Subj: NAVMED-36, Ration Record

Ref: (a) BUMED Cir Ltr No. 50-58
(b) BUMED ltr BUMED-2323, L16-8 of 15 Jun 50
(c) BUMED Cir Ltr No. 51-4
(d) BUMED Cir Ltr No. 51-17
(e) BUMED Cir Ltr No. 51-49
(f) BUMED Cir Ltr No. 51-71
(g) BUMED Cir Ltr No. 50-67
(h) BUMED Cir Ltr No. 51-26
(i) BUMED Cir Ltr No. 51-29
(j) BUMED Cir Ltr No. 51-51
(k) ALNAV 51-51
(l) BUMED Cir Ltr No. 51-92
(m) BUMED Cir Ltr No. 49-168

This letter, which will not be printed in the Navy Department Bulletin, cancels references (a) through (f). Reference (g) is modified by deletion of paragraph 17. Reference (h) is modified by deletion of "Lines 28, 29, 30, 31, 45 and 49" and substitution of "Lines 23, 24, 45 and 46" in subparagraph 2i. Reference (i) is modified by deletion of the last sentence of paragraph 3 and substitution of the following: "Naval hospitals shall report this personnel classification on Line 58 of the NavMed-36, Ration Record." References (g) through (j) are further modified by correcting references thereto as appropriate in view of these revised instructions. References (k) and (l) prescribe the value of the hospital ration, sold meal rates, and hospitalization rates for the current fiscal year. Reference (m) remains in effect and is pertinent only insofar as classification of reserve personnel under the provisions of Public Law 108 is concerned. Cancellations, supersedures, and modifications are effective 1 July 1951. An initial supply of the revised NavMed-36 is being forwarded to each addressee. Report for the month of July, 1951, shall be resubmitted at the earliest practicable date, using the revised form in accordance with these instructions.

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BUMED CIRCULAR LETTER 51-118 15 August 1951

To: All Activities with Medical Department Personnel Attached

Subj: Medical Department exhibit activities; coordination of

Ref: (a) SecNav Ltr 50-465, NDB Jan-June 1950, page 62

1. All inquiries involving Medical Department participation at civilian meetings of national, regional, or sectional importance that may warrant the presentation

of an exhibit shall be submitted via BuMed to the Chief of Information (formerly the Director of Public Relations) in accordance with the provisions contained in reference (a).

2. An invitation to present an exhibit at a public function shall not be accepted until:

(a) Clearance has been obtained from the Chief of Information, Department of the Navy, Washington, D. C.

(b) An appropriate exhibit, or funds for exhibit construction are available.

(c) Personnel to attend and demonstrate the exhibit are available.

(d) Funds to defray the cost of per diem and travel for demonstrator personnel are available.

3. Should it be desired to accept an invitation to present an exhibit, the letter requesting presentation authority should contain the following information:

(a) Whether or not professional assistance from BuMed will be required in the planning and designing of the exhibit.

(b) Amount of financial assistance required, if any, to defray the cost of:

(1) Exhibit construction.

(2) Temporary additional duty orders for presentation personnel.

H. L. Pugh

The above letter will not be printed in the Navy Department Bulletin.

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BUMED CIRCULAR LETTER 51-119 22 August 1951

From: Chief, Bureau of Medicine and Surgery
To: All activities under management control of the Bureau of Medicine and Surgery

Subj: Procedure for preparation and submission of work projects under the Specific Work Request Program

Ref: (a) BuMed C/L No. 48-145
(b) BuMed C/L No. 49-27

Encl: (1) Station Project Request
(2) Local Request for Estimate
(3) Check-off List

References (a) and (b) are canceled. This circular letter, which will not be printed in the Navy Department Bulletin, sets forth the procedures necessary for the preparation and submission of work projects under the Specific Work Request Program.

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Duty With the Atomic Bomb Casualty Commission

The Atomic Bomb Casualty Commission sponsored by the National Academy of Sciences and the Atomic Energy Commission conducts two clinical laboratories at Hiroshima and at Nagasaki. The program is carried on in the field by approximately 100 physicians and 900 supporting personnel. Six of the American physicians in residence are certified by their Specialty Boards. Elective courses in biometrics and radiobiology are available to the resident staff. Laboratory equipment is highly adequate. Working and living conditions are desirable. A knowledge of the Japanese language is advantageous but not mandatory.

Applications for duty with the ABCC are desired as soon as possible from interested officers in the ranks of Lieutenant Junior Grade or Lieutenant, MC, USN, and should be addressed via official channels to the Chief of the Bureau of Medicine and Surgery. (Personnel Div., BuMed)

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NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
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